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Editorial Comment

The capacity of the immune system to control cancer

Leif Håkansson

Biotherapy Development Association, Department of Oncology, University Hospital MAS, SE-205 02 Malmö, Sweden

ARTICLE INFO

Article history:
Received 4 June 2009
Accepted 8 June 2009
Available online 14 July 2009

Immunostimulatory treatment of cancer, using cytokines and therapeutic vaccination, has been investigated for several decades but with very limited success. In this issue of the *European Journal of Cancer*, Alexander Eggermont highlights these problems in an article entitled: 'Therapeutic vaccines in solid tumours: can they be harmful?' The poor response to immunotherapy is a paradox as convincing experimental and clinical data now strongly indicate that the immune system plays a major role in cancer control. The immune surveillance concept[1] was abandoned more than 30 years ago mainly for the wrong reasons. The expected increased incidence of malignant tumours in immunocompromised animals such as nude mice was never confirmed. It is, however, now clear that these animal models were in reality not profoundly immunocompromised, but were still able to mount a significant anti-tumour immune reactivity. When severely immunocompromised transgenic mice of the Stat 1 –/–, IFNgR –/–, or RAG2 –/– genotypes were studied later on, the tumour incidence and the immunogenicity of cancers growing in such animals strongly supported the existence of immune mediated anti-cancer reactivity with the capacity to control cancer development. Based on these results, the immunoediting model was developed[2] with an early elimination phase (elimination of tumour cells by the immune system), followed by an equilibrium phase (a balance phase when tumour progression is still controlled by the immune system) and an escape phase (when the tumour grows progressively).

The absence of an enhanced incidence of adenocarcinoma and squamous cell carcinoma in therapeutically immunosuppressed allo-organ transplanted patients was considered to be another strong argument against the immune surveillance concept. However, it now seems clear that these cancers, at an early stage, have the capacity to down-regulate the anti-tumour immune reactivity. Crucial immune parameters, such as the presence of dendritic cells[3], expression of the ζ-chain of the T-cell receptor[4] and expression of CD28,[5] were often dysregulated in the sentinel node, even in the absence of lymph node metastasis. Similarly, the expression of several cell surface receptors on circulating monocytes of stage II breast cancer patients were found to be missing.[6] In addition, the occurrence of regulatory T-cells at an early stage was found to correlate to prognosis.[7] Thus, further therapeutic immunosuppression in these cancers will not change the course of the disease.

The importance of immune mediated cancer control is further supported by the often found positive correlation between the occurrence of tumour infiltrating lymphocytes and prognosis[8–12] and a negative correlation between the occurrence of immunosuppressor cells, such as regulatory T-cells, and prognosis.[7–15] In particular, the ratio between effector cells and suppressor cells can be of predictive value.[16]

Determination of crucial immune parameters related to tumour progression might provide significant prognostic information. Clinchy et al.[17] showed that dysregulation of the immune system in cancer, with an enhanced capacity to produce interleukin-6 (IL-6), correlates to poor prognosis in radically resected colorectal cancer patients. No cancer related deaths were found in the group of Stage III tumours with

E-mail address: canimguide@gmail.com
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2009.06.002

normal production of IL-6. Similarly, Galon et al.[18] have shown that T-cell immune parameters strongly correlate to prognosis in colorectal cancer patients. It could then be argued that a subset of good prognosis cancers has been identified by these immune parameters and that the good prognosis is not due to an immune mediated cancer control. However, it is well-known that early resection of a cancer has a major influence on the chance to achieve cure. Thus, the good prognosis cancers identified by these immune tests would have escaped immune mediated control if they had been left to progress. The prognostic value of immune parameters was, in these papers, considered to be superior to the prognostic information obtained by the classic TNM classification. These results strongly support the importance of the immune system in cancer control.

The immunoediting model predicts that major changes have taken place when tumours progress from the equilibrium phase to the escape phase. In animal models it is clearly shown that the immunologically sculpted tumours are less immunogenic, but also that immunosuppression plays a major role when tumours enter the escape phase.[19] As discussed above, it is obvious that the immune system is still of major importance for human cancer control.

Changes take place in the immune system when tumours progress from the equilibrium phase to the escape phase, with a gradual increase of cancer related immunosuppression. Only the subset of patients who still have limited immunosuppression, with some crucial immune functions left, will have the capacity to respond to immunotherapy. The response rate to immunotherapy will consequently be low as the majority of patients with progressively growing metastatic cancers have a far too severe immunosuppression to respond. This view is compatible with the repeatedly found correlation between the occurrence of tumour infiltrating lymphocytes[20–22] or a gene signature in tumour biopsy pretreatment[23] and response to immunotherapy.

The immune system has the capacity to control cancer! Why doesn't it work?

The immune system is finely tuned to detect and eradicate foreign structures, 'non-self', and, at the same time, avoid over-reactivity with destruction of normal tissues resulting in autoimmune or chronic inflammatory diseases. These extensive down-regulatory control mechanisms, if pathologically triggered, can efficiently block the immune system, as seen in cancer related immunosuppression.

Several tumour-cell related mechanisms whereby tumours evade immune mediated control have been described, e.g. decreased tumour cell immunogenicity and tumour cell resistance to apoptosis. It is often argued that tumour associated antigens are weak, self antigens against which it is difficult to obtain strong immune responses. However, even if tumour cells are transfected with strong antigens, the tumour milieu has the capacity to suppress the immune response.[24] A multitude of mechanisms down-regulating immune reactivity have been described, but malignant tumours primarily have only a very limited number of ways to induce immunosuppression: via Inflammation, hypoxia, phagocytosis of apoptotic tumour cells and Fc-receptor modulation. These *primary mechanisms* will result in a cascade of other, *secondary mechanisms*. Early on, a beneficial inflammatory reaction controlling the cancer is elicited (elimination phase of the immunoediting model). Inflammatory reactions should then be down-regulated once the eliciting agent is eradicated. In cancer, however, the eliciting agent, the cancer, is often not eradicated but persists, creating a chronic inflammation which continues to stimulate down-regulatory mechanisms. The dysregulated cytokine profile, enhanced proteolytic activity and enhanced production reactive oxygen species being of major importance. In addition to this, hypoxia, phagocytosis of apoptotic tumour cells and Fc-receptor cross-linking all have profound effects on down-regulation of immune reactivity. All these mechanisms are normally in place in order to control over-reactivity and avoid autoimmunity. In progressively growing metastatic cancer, these mechanisms together create a 'full-blown' immunosuppression.

According to the immunoediting model, a balance (equilibrium phase) can, however, be achieved, with no clinical tumour progression for a long period of time. After radical surgery, very long recurrence free intervals are seen, indicating that a 'second equilibrium phase' has been induced. At the transition between the equilibrium and escape phases it is reasonable that, initially, only some of the suppressor mechanisms are active and should even be reversible once they are identified.

Stimulation of an immune system, which is triggered to down-regulate immune reactivity, will of course carry the risk that the down-regulatory, inhibitory mechanisms are stimulated, worsening immunosuppression and further facilitating tumour escape. This mechanism is a likely explanation for the poor results found in the vaccination arms, compared to the control arms, in some of the studies described by Eggermont. These results highlight the need to identify and control immunosuppressor mechanisms before immunostimulatory treatment is initiated.

Based on the poor results summarised in the paper by Eggermont, it seems obvious that immunostimulatory treatment such as vaccination alone will not be able to achieve immune mediated cancer control. The therapeutic strategy to be applied is, based on the immunosuppressor mechanisms discussed above, highly dependent on whether we intend to treat patients with progressively growing metastatic cancer or radically resected cancer patients in a 'second equilibrium' phase.

The initial changes in the immune system when tumours escape and take a more aggressive course are not fully understood which necessitates a structured analysis of these mechanisms and how they can be counteracted. Due to the poor efficacy of immunostimulatory treatment during the past decades, it seems reasonable to postulate that there are other so far unidentified suppressor mechanisms. It is therefore of great importance that immunotherapy and vaccination trials are closely monitored by using relevant immune parameters. The selection of these parameters is of crucial importance. Determination of cytotoxic T-cells in peripheral blood, using ELISPOT or tetramer staining, is an excellent method to demonstrate that an immune response has been achieved. This does not, however, usually correlate to tumour regression.[25] Additional, pivotal immune parameters are: recruitment of effector cells to the tumour, migration of these cells from the intra-tumoural stromal areas close to the tumour cells, and lysis of tumour cells. These parameters can easily be determined

provided that tumour material can be obtained. Imaging techniques for determination of immune cell recruitment are now being developed. Clinical monitoring only is far too blunt a technique to increase our knowledge – it will not even enable us to discriminate between a total failure of the treatment strategy and an initial anti-tumour reactivity followed by the development of immunosuppressor/resistance mechanisms. Both these scenarios will, in the absence of close monitoring, be registered as total failures.

Two therapeutic strategies giving some hope for the future are mentioned by Eggermont: immunomodulation by antibodies directed to immune cell receptors and lymphodepletion in combination with immunostimulation. As the former strategy is close to the control of autoimmunity, there is an obvious risk that such diseases will complicate the cancer treatment. A careful analysis of immune parameters in the successful lymphodepletion strategy should give valuable insight into how the efficacy of immunotherapy can be improved. It also seems reasonable to select patients for treatment based on parameters which have been demonstrated to have predictive value for the outcome of immunotherapy, e.g. occurrence of tumour infiltrating lymphocytes[20–22] or a gene signature in tumour biopsy pre-treatment.[23]

It can thus be concluded that the immune system plays a major role in cancer control, that the immunoregulatory mechanisms which suppress immune mediated cancer control are not yet fully understood, and that a structured analysis of these immunoregulatory mechanisms will create the basis for significantly improved efficacy of immunostimulatory treatment.

Conflict of interest statement

None declared.

REFERENCES

1. Burnet FM. The concept of immunological surveillance. *Prog Exp Tumor Res* 1970;**13**:1–27.
2. Dunn GP, Old LJ, Schreiber RD. The immunobiology of cancer immunosurveillance and immunoediting. *Immunity* 2004;**21**:137–48.
3. Cochran AJ, Morton DL, Stern S, et al. Sentinel lymph nodes show profound downregulation of antigen-presenting cells of the paracortex: implications for tumor biology and treatment. *Mod Pathol* 2001;**14**:604–8.
4. Schüle J, Bergkvist L, Håkansson L, Gustafsson B, Håkansson A. Down-regulation of the CD3-zeta chain in sentinel node biopsies from breast cancer patients. *Breast Cancer Res Treat* 2002;**74**:33–40.
5. Schüle JM, Bergkvist L, Håkansson L, Gustafsson B, Håkansson A. CD28 expression in sentinel node biopsies from breast cancer patients in comparison with CD3-zeta chain expression. *J Transl Med* 2004;**2**:45.
6. Wolfram RM, Budinsky AC, Brodowicz T, et al. Defective antigen presentation resulting from impaired expression of costimulatory molecules in breast cancer. *Int J Cancer* 2000;**88**:239–44.
7. Petersen RP, Campa MJ, Sperlazza J, et al. Tumor infiltrating Foxp3+ regulatory T-cells are associated with recurrence in pathologic stage I NSCLC patients. *Cancer* 2006;**107**:2866–72.
8. Atreya I, Neurath MF. Immune cells in colorectal cancer: prognostic relevance and therapeutic strategies. *Expert Rev Anticancer Ther* 2008;**8**(4):561–72.
9. Nelson BH. The impact of T-cell immunity on ovarian cancer outcomes. *Immunol Rev* 2008;**222**:101–16.
10. Ohtani H. Focus on TILs: prognostic significance of tumor infiltrating lymphocytes in human colorectal cancer. *Cancer Immun* 2007;**7**:4.
11. Ruffini E, Asioli S, Filosso PL, et al. Clinical significance of tumor-infiltrating lymphocytes in lung neoplasms. *Ann Thorac Surg* 2009;**87**:365–71.
12. Yu P, Fu YX. Tumor-infiltrating T lymphocytes: friends or foes? *Lab Invest* 2006;**86**:231–45.
13. Perrone G, Ruffini PA, Catalano V, et al. Intratumoural FOXP3-positive regulatory T cells are associated with adverse prognosis in radically resected gastric cancer. *Eur J Cancer* 2008;**44**:1875–82.
14. Bates GJ, Fox SB, Han C, et al. Quantification of regulatory T cells enables the identification of high-risk breast cancer patients and those at risk of late relapse. *J Clin Oncol* 2006;**24**:5373–80.
15. Wolf D, Wolf AM, Rumpold H, et al. The expression of the regulatory T cell-specific forkhead box transcription factor FoxP3 is associated with poor prognosis in ovarian cancer. *Clin Cancer Res* 2005;**11**:8326–31.
16. Hodi FS, Butler M, Oble DA, et al. Immunologic and clinical effects of antibody blockade of cytotoxic T lymphocyte-associated antigen 4 in previously vaccinated cancer patients. *Proc Natl Acad Sci USA* 2008;**105**:3005–10.
17. Clinchy B, Fransson A, Druvefors B, et al. Preoperative interleukin-6 production by mononuclear blood cells predicts survival after radical surgery for colorectal carcinoma. *Cancer* 2007;**109**:1742–9.
18. Galon J, Costes A, Sanchez-Cabo F, et al. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. *Science* 2006;**313**:1960–4.
19. Teng MW, Swann JB, Koebel CM, Schreiber RD, Smyth MJ. Immune-mediated dormancy: an equilibrium with cancer. *J Leukoc Biol* 2008;**84**:988–93.
20. Håkansson A, Gustafsson B, Krysander L, et al. Biochemotherapy of metastatic malignant melanoma. Predictive value of tumour-infiltrating lymphocytes. *Br J Cancer* 2001;**85**:1871–7.
21. Håkansson A, Gustafsson B, Krysander L, Håkansson L. Tumour-infiltrating lymphocytes in metastatic malignant melanoma and response to interferon alpha treatment. *Br J Cancer* 1996;**74**:670–6.
22. Donskov F, Bennedsgaard KM, Von Der Maase H, et al. Intratumoural and peripheral blood lymphocyte subsets in patients with metastatic renal cell carcinoma undergoing interleukin-2 based immunotherapy: association to objective response and survival. *Br J Cancer* 2002;**87**:194–201.
23. Louahed J, Gruselle O, Gaulis S, et al. *J Clin Oncol* 2008;**26**. abstract 9045.
24. Yu P, Lee Y, Liu W, et al. Intratumor depletion of CD4+ cells unmasks tumor immunogenicity leading to the rejection of late-stage tumors. *J Exp Med* 2005;**201**:779–91.
25. Nielsen MB, Marincola FM. Melanoma vaccines: the paradox of T cell activation without clinical response. *Cancer Chemother Pharmacol* 2000;**46**(Suppl.):S62–6.